REMARKS

A check for $860 for the fees for filing of an RCE ($385) and for the fee for a three-month extension of time ($475) accompanies this response. Any fee that may be due in connection with this application may be charged to Deposit Account No. Deposit Account No. 06-1050. If a Petition for extension of time is needed, this paper is to be considered such Petition. A Notice of Change of Address accompanies this response.

Claims 70, 72-79, 92-94, 123, 124, 127-133 and 135-138 are pending in this application. Claims 11, 13-15, 44 and 75 are amended herein to more particularly point out and distinctly claim the subject matter. The amendments made herein presume entry of the amendment submitted in the Amendment After Final, mailed May 27, 2004.

The specification is amended herein to incorporate material at page 12 of the instant specification from International Patent Application PCT/US89/04741, which published as WO 90/04652 on May 3, 1990, page 3, line 37 through page 6, line 9, that had been incorporated by reference in its entirety in the instant application (see page 12, lines 2-3). A Declaration, executed by Applicant's representative, stating that the amendatory material is the material incorporated by reference, is provided. No new matter is added.

Claims 70, 74 and 124 are amended to replace the recitation "variable" with the recitation –random–, basis for which is found throughout the specification (see, *e.g.*, page 20, line 25 through page 21, line 8 and the original claims as filed). The amendment restores the recitation "random" as originally claimed. Claim 75 is further amended to more distinctly claim the subject matter by replacing the recitation "terminus" with the recitation –5'-terminus or 3'-terminus–. Claim 73 is amended to correct a minor grammatical error.

Claims 75 and 137 are amended herein to more distinctly recite that the nucleic acids in the array are fixed to a solid support. Basis for the amendment is found throughout the application (for example, see page 6, lines 6-7 and page 8, lines 5-7). Claim 124 is amended to replace the recitation "4^n" with "-4^R-". Basis

for the amendment is found throughout the specification (for example, see page 11, lines 21-23 and the original claims as filed). Claim 127 is amended to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (for example, see page 12, lines 3-6). Claim 136 is amended to replace the recitation "constant portion" with the recitation –double-stranded portion–, basis for which is found throughout the specification (for example, see page 20, lines 1-2). Therefore, no new matter is added.

REJECTION OF CLAIMS 70, 72, 73 AND 77-79 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 70, 72, 73 and 77-79 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject matter at the time of filing of the application. The Examiner alleges that the specification does not provide adequate support for the recitation "wherein the variable sequence is not at the terminus" in claim 70.

Applicant respectfully traverses the rejection.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific [claimed embodiment] *Vas-Cath, Inc. v. Mahurkar*, at 1115, quoting *In re Ruschig*, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir. 1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application

may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Furthermore, the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *inhaec verba*) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2173.05(i) recites "that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support. *Ex parte Parks,* 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993)." *Parks* states that:

> The initial burden of establishing a prima facie basis to deny patentability to a claimed invention is always upon the Examiner. *Id.* at 1236. "In rejecting a claim under the first paragraph of 35 U.S.C. 112 for lack of adequate descriptive support, it is incumbent upon the Examiner to establish that the originally-filed disclosure would not have reasonably conveyed to one having ordinary skill in the art that an appellant had possession of the now claimed subject matter." *Id.*
>
> The guidelines promulgated by the U.S. PTO embody these rules:
>
> In rejecting a claim, set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:
>
> > (1) identify the claim limitation not described; and
> >
> > (2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

CLAIM 70

Claim 70 is directed to an array of nucleic acid probes, where each probe has a double-stranded portion, a terminal single-stranded portion, and a random nucleotide sequence within the single-stranded portion, where the random

sequence is not at the 5'-terminus or the 3'-terminus. Claims 72, 73 and 77-79 ultimately depend from claim 70 and are directed to various embodiments thereof.

ANALYSIS

Claims 70, 72, 73 and 77-79 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification. The Examiner contends that the addition of the limitation that the random sequence is not at the terminus is a negative limitation without support. MPEP §2173.05(i) was cited in support of this statement. MPEP §2173.05(i) notes "that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support. MPEP §2173.05(i) further states that

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternate elements are positively recited in the specification, they may be explicitly excluded in the claims, See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining.").

The specification teaches that the random sequence is within the single-stranded sequence. For example, page 6, lines 3-6 teaches:

> One embodiment of the invention is directed to arrays of 4^R different nucleic acid probes wherein each probe comprises a double-stranded portion of length D, a terminal single-stranded portion of length S, and **a random nucleotide sequence within the single-stranded portion** of length R. [*emphasis added*]

See also page 6, lines 16-24, which teaches:

> Another embodiment of the invention is directed to methods for creating arrays of probes comprising the steps of synthesizing a set of nucleic acids each containing a random internal sequence of length R flanked by the cleavage sites of a restriction enzyme, synthesizing a set of primers each complementary to a non-random sequence of the nucleic acid, hybridizing the two sets together to form hybrids, extending the sequence of the primer by polymerization using the nucleic acid as a template, and cleaving the hybrids with the restriction enzyme to form an array of probes with a double-stranded portion and a single-stranded portion and with **the random sequence within the single stranded portion.** [*emphasis added*]

Applicant respectfully submits that, when given its ordinary meaning (for example, see *Merriam Webster's Collegiate Dictionary*, Tenth ed., 1995, page 1359), the word "within" as used in the recitation "variable nucleotide sequence within the single-stranded region" connotes being contained in the single-stranded portion of the probe, including being in the interior of or inside of the single-stranded region. The specification teaches the single-stranded region can be at the 3'- or the 5'-terminus (for example, see page 24, lines 24-25). The specification teaches embodiments where the random sequence is at a terminus. For example, page 6, lines 10-15 teaches:

> Another embodiment of the invention is directed to methods for creating arrays of probes comprising the steps of synthesizing a first set of nucleic acids each comprising a constant sequence of length C at the 3'-terminus, and **a random sequence of length R at the 5'-terminus**, synthesizing a second set of nucleic acids each comprising a sequence complimentary to the constant sequence of the first nucleic acid, and hybridizing the first set with the second set to form the array.

Table 5 provides examples of a random sequence at the 3'-terminus (see page 48, lines 19-24). It is respectfully submitted that, at the time of application, applicant appreciated and was in possession of an array of probes where the random sequence is within the single-stranded region either at a terminus of the single-stranded region or in the interior of the single-stranded region. Table 5 on page 48 illustrates this. In the probes having a 5 bp overlap, the random sequence is at the 3'-terminus:

3'-CTA CTA GGC TGC GTA GTC
5'-biotin-GAT GAT CCG ACG CAT CAG AGC **TC**-3'

3'-CTA CTA GGC TGC GTA GTC
5'-biotin-GAT GAT CCG ACG CAT CAG AGC **TT**-3'

In the probes having a 6 bp overlap, the random sequence is within the single-stranded region but is not at a terminus:

3'-CTA CTA GGC TGC GTA GTC
5'-biotin-GAT GAT CCG ACG CAT CAG A**GC** TCT-3'

3'-CTA CTA GGC TGC GTA GTC
5'-biotin-GAT GAT CCG ACG CAT CAG A**GT** TCT-3'

Thus, a person of skill in the art would recognize that applicant had possession of an array of probes with a double-stranded portion and a single-stranded portion where the random sequence within the single stranded portion is at a terminus or is contained within the single-stranded region. As amended, claim 70 is directed to the embodiment of an array of probes having a double-stranded portion and a single-stranded portion and a random sequence within the single-stranded portion but not at its terminus. Applicant respectfully submits that there is no basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of such as array in view of the disclosure of the application as filed. Further, because the element of having a random sequence at the 3'-terminus and the element of having a random sequence at the 5'-terminus are positively recited in the specification, they may be explicitly excluded in the claims.

In view of the above remarks that make clear that the claims as amended were within the possession of the applicant at the time of filing the instant application, applicant respectfully requests that the rejection of claims 70, 72, 73 and 77-79 under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

REJECTION OF CLAIMS 74-76, 92-94, 123, 124 AND 136 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 74-76, 92-94, 123, 124 and 136 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject matter at the time of filing of the application. The Examiner alleges that the specification does not provide adequate support for the recitation "a variable terminal nucleotide sequence of between about 3-10 nucleotides in length" in claim 74.

Applicant respectfully traverses the rejection.

RELEVANT LAW

See related section above.

The Instant Claims

Claim 74 is directed to an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and an oligonucleotide of about 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid.

ANALYSIS

While not conceding the propriety of this rejection, it is respectfully submitted that this rejection is obviated by the amendment of claim 74 herein that replaces the recitation "variable" with the recitation –random– as originally claimed. The specification teaches an array of probes having a random terminal nucleotide sequence of between about 3-10 nucleotides in length. For example, the specification teaches at page 20, line 28 through page 21, line 8 that in one embodiment, the claimed subject matter

> is directed to a method for creating probe arrays comprising the steps of synthesizing a first set of nucleic acids each comprising a constant sequence of length C at a 3'- terminus and a random sequence of length R at a 5'-terminus, synthesizing a second set of nucleic acids each comprising a sequence complimentary to the constant sequence of each of the first nucleic acid, and hybridizing the first set with the second set to create the array. Preferably, the nucleic acids of the first set are each between about 15-30 nucleotides in length and the nucleic acids of the second set are each between about 10-25 nucleotides in length. Also preferable is that C is between about 7-20 nucleotides and R is between about 3-10 nucleotides.

Hence, the specification provides adequate description for an array of probes that include a random nucleotide sequence between about 3-10 nucleotides. It is

respectfully submitted that the skilled artisan would recognize that an array of probes having a random nucleotide sequence of a length between about 3-10 nucleotides as instantly claimed in claim 74 was contemplated at the time of filing of this application. No new matter has been added.

REJECTION OF CLAIMS 127-133, 135, 137 AND 138 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 127-133, 135, 137 and 138 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject matter at the time of filing of the application. The Examiner alleges that the specification does not provide adequate support for the recitations "each probe comprises a predetermined sequence of fixed and non-fixed positions; and the array is divided into subarrays, wherein for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base" in claim 127. The Examiner alleges that Macevicz does not provide basis for the recitations, and contends that "applicant appears to be extrapolating from Macevicz terminology and structure not clearly defined by the reference" and the amendments thus allegedly constitute new matter. The Examiner further states in the Advisory Action, mailed June 10, 2004, that "applicant appears to be stating that the recitations supported by Macevicz are "essential subject matter" and urges that essential subject matter cannot be incorporated by reference.

Applicant respectfully traverses the rejection.

RELEVANT LAW

See related section above.

THE INSTANT CLAIMS

Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the

opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the probes are divided into four subsets, wherein for each subset, one of the four nucleic acid bases is selected and occupies a defined number of positions in each probe and all other bases except the selected base occupy the remaining positions. Claims 128-133, 135, 137 and 138 depend from claim 127 and are directed to various embodiments thereof.

ANALYSIS

As a preliminary matter, applicant respectfully submits that as amended, claim 74 does not recite "each probe comprises a predetermined sequence of fixed and non-fixed positions," and hence the rejection as directed to that recitation is moot. It is respectfully submitted that, at the time of application, applicant appreciated and was in possession of an array of probes as instantly claimed in claim 74.

The specification teaches that the probes are divided into four subsets, where for each subset, one of the four nucleic acid bases is selected and occupies a defined number of positions in each probe and all other bases except the selected base occupy the remaining positions. For example, the instant specification teaches at page 12, lines 3-9 that:

> The probes are divided into four subsets. **In each, one of the four bases is used at a defined number of positions and all other bases except that one on the remaining positions.** Probes from the first subset contain two elements, A and non-A (A = adenosine). For a nucleic acid sequence of length k, there are $4(2^{k-1})$, instead of 4^k probes. Where k = 8, a set of probes would consist of only 1020 different members instead of the entire set of 65,536. The savings in time and expense would be considerable.

Hence, the specification provides adequate support for the recitation "the probes are divided into four subsets, wherein for each subset, one of the four nucleic acid bases is selected and occupies a defined number of positions in each probe and all other bases except the selected base occupy the remaining positions" in claim 127. Hence, applicant is not "extrapolating from Macevicz terminology and structure not clearly defined by the reference" as alleged by the Examiner. The

claimed subject matter is supported by the specification. Thus, applicant was in possession of an array of probes having the claimed characteristics at time of application. Therefore, the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the claimed subject matter. No new matter has been added.

REBUTTAL TO EXAMINER'S ARGUMENT

The Examiner urges in the Advisory Action that applicant appears to be stating that the recitations supported by Macevicz are "essential subject matter" and contends that reliance on Macevicz is improper because essential subject matter relied upon cannot be incorporated by reference. MPEP 608.01(p)(I)(A) defines "essential material" as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)." Nonessential subject matter is defined as "subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art." *Id.* It is respectfully submitted that Macevicz provides background for the claimed subject matter and illustrates the state of the art, particularly of degenerated probes, at the time the original application was filed. Thus, because Macevicz is not relied upon to describe the claimed invention, to provide an enabling disclosure of the claimed invention, or to describe the best mode, Macevicz is not relied upon for "essential material."

As discussed above, the instant application provides direct basis for the recitation "the probes are divided into four subsets, wherein for each subset, one of the four nucleic acid bases is selected and occupies a defined number of positions in each probe and all other bases except the selected base occupy the remaining positions" in claim 127. Thus, applicant does not rely on Macevicz for the subject matter claimed in claim 127.

Notwithstanding the above and not conceding that the subject matter taught by Macevicz is essential subject matter, in order to advance the application to allowance, applicant amends the specification herein to explicitly incorporate that which is incorporated by reference in the specification, by including the disclosure

of Macevicz (International Patent Application PCT/US89/04741) from page 3, line 4 through page 6, line 9, thereby obviating this objection.

REJECTION OF CLAIMS 75, 136 AND 137 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 75, 136 and 137 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter.

This rejection is respectfully traversed.

RELEVANT LAW

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). A claim is not indefinite when one skilled in the art would understand all of the language in the claims when read in light of the specification.

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

THE CLAIMS

Claim 75 is directed to the array of claim 74, where the nucleic acids in the array are fixed to a solid support selected from the group consisting of plastics, ceramics, metals, resins, gels, membranes, and chips.

Claim 136 is directed to the array of claim 74, where the double-stranded portion of each probe includes an enzyme recognition site.

Claim 137 is directed to the array of claim 127, where the nucleic acids in the array are fixed to a solid support.

ANALYSIS

CLAIMS 75 AND 137

The Examiner alleges that it is unclear whether the recitation "which is fixed to a solid support" in both claim 75 and claim 137 is intended to limit the nucleic acid probes or the claimed array. Applicant respectfully submits that this rejection is obviated by the amendment of claims 75 and 137 herein to recite "wherein the nucleic acids of the array are fixed to a solid support."

CLAIM 136

The Examiner alleges that there is no antecedent basis for the recitation "the constant portion" in claim 74. Applicant respectfully submits that this rejection is obviated by the amendment of claim 136 herein, which replaces the recitation "the constant portion" with the recitation –the double-stranded portion–, for which claim 74 provides antecedent basis.

REJECTION OF CLAIMS 75, 134 AND 135 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

In the Advisory Action, mailed June 10, 2004, the Examiner states in the section on page 2 captioned "Continuation of 3" that if entered, the amendments to dependent claims 75, 134 and 135 would overcome the rejection under 35 U.S.C. §112, second paragraph. Applicant respectfully submits that claim 134 is a cancelled claim. Applicant also submits that, in the Amendment After Final, mailed May 27, 2004, claim 75 was amended, but claim 135 was not amended in the Amendment After Final. Further, neither claim 134 nor claim 135 was rejected under 35 U.S.C. §112, second paragraph. Applicant respectfully submits that claims 75, **136** and **137**, as discussed above, were rejected under 35 U.S.C. §112, second paragraph in the Office Action, mailed February 18, 2004. Applicant respectfully requests clarification.

THE REJECTION OF CLAIMS 70, 72, 74, 76-79, 92-94, 124, 127, 129-131, 133 AND 135-137 UNDER 35 U.S.C. § 102(e)

Claims 70, 72, 74, 76-79, 92-94, 124, 127, 129-131, 133 and 135-137 are rejected under 35 U.S.C. § 102(e) as anticipated by Deugau *et al.* (U.S. Patent

No. 5,508,169) because Deugau *et al.* allegedly discloses an array of nucleic acid probes having a double-stranded portion at the 3'-terminus and a single-stranded portion at the 5'-terminus (Fig. 2; column 11, lines 14-25; and column 9, lines 28-42). The Examiner alleges that the claims have been amended to introduce numerous method steps for making the array of probes (e.g., hybridizing, ligating, predetermined, divided, selected) and that these method limitations in the apparatus claims are given little patentable weight because the determination of patentability is based on the product itself and not on its method of production.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 70 is directed to an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion, and a random nucleotide sequence within the single-stranded portion, where the random

sequence is not at the 5'-terminus or the 3'-terminus. Claims 72, 73 and 77-79 depend from claim 70 and are directed to various embodiments thereof.

Claim 74 is directed to an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and an oligonucleotide of about 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Claims 75, 76, 92-94, 123, 124 and 136 depend from claim 74 and are directed to various embodiments thereof.

Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the probes are divided into four subsets, wherein for each subset, one of the four nucleic acid bases is selected and occupies a defined number of positions in each probe and all other bases except the selected base occupy the remaining positions. Claims 128-133, 135, 137 and 138 depend from claim 127 and are directed to various embodiments thereof.

Disclosure of Deugau *et al.*

Deugau *et al.* discloses indexing linkers that have single-stranded portions on both ends or on only one end. The reference discloses that the double-stranded portion can be at either the 3'-terminus or at the 5'-terminus. Deugau *et al.* discloses that the indexing linkers have a protruding single strand of a unique sequence of 3, 4, or 5 nucleotides, and that neither single-stranded end functions as a restriction endonuclease recognition site. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce overhangs on each end of a fragment (col. 7, lines 48-60).

Differences between the claimed subject matter and the disclosure of Deugau *et al.*

1. As Directed to Claims 70, 72, 73 and 77-79

Applicant respectfully submits that the rejection as applied to the recitation "variable" is obviated by the amendment of claim 70 herein. Pending claims 70, 72, 73 and 77-79 no longer include the recitation "variable."

Deugau *et al.* does not disclose a probe that includes a random nucleotide sequence that is not at the terminus of the single-stranded portion. The Examiner alleges that claim 33 of Deugau *et al.* discloses the array of instant claim 70. Applicant respectfully disagrees. Claim 33 of Deugau *et al.* states

> 33. In a polymerase chain reaction kit comprising: heat source, oligonucleotide primers, DNA polymerase and a mixture of all four deoxynucleotide precursors, wherein the improvement comprises:
>
> a panel for obtaining indexed DNA fragments from a mixture of DNA fragments, for identifying, isolating, mapping, amplifying, or sequencing said fragments,
>
> said panel comprising a set of indexing linkers, each said indexing linker being a DNA duplex having one 3'- or 5'-protruding single strand of a length corresponding to the 3'- or 5'-protruding single strand of the cleavage site of a Type IIS restriction endonuclease or a restriction endonuclease recognizing interrupted palindromic sequences, wherein said set comprises a collection of indexing linkers whose 3'- or 5'-protruding single strands collectively encode up to all possible permutations and combinations of the nucleotides, A, C, G and T, and wherein said indexing linkers are physically separated from each other on the basis of the identity of their 3'- or 5'-protruding single strand.

Applicant respectfully submits that claim 33 does not disclose an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion, and a random nucleotide sequence that is <u>not at the 5'-terminus or the 3'-terminus</u> of the single-stranded region.

Figure 2 of Deugau *et al.* illustrates a set of probes that have variable sequences at the **terminus** of the probes. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce protruding overhangs on each **end** of a fragment (col. 7, lines 48-60). Because the restriction endonucleases produce terminal overhangs, the index linkers of

Deugau *et al.* do not include a random sequence that is not terminal. Thus, Deugau *et al.* does not disclose a random sequence within the single-stranded portion that is not at a terminus, and hence does not disclose every element of the claimed subject matter of claim 70 and its dependent claims. Therefore, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 70, 72, 73 and 77-79.

2. As Directed to Claims 74-76, 92-94, 123, 124 and 136

The Examiner alleges that claims 74-76, 92-94, 123, 124 and 136 include "numerous method steps for making the array of probes, *e.g.* hybridizing, ligating" and "that patentability of a product is based on the product, not the method of making the product" and contends that the claimed arrays are interpreted based on the resulting product. As a preliminary matter, applicant respectfully submits that none of claims 74-76, 92-94, 123, 124 or 136 includes "hybridizing" or "ligating" as a recitation. Claim 74 includes the recitations "the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion" and "the oligonucleotide is ligated to the variable sequence of the second nucleic acid."

The instant claims do not have method or process step limitations. The Examiner is reminded that

> 35 U.S.C. 101 defines four categories of inventions that Congress deemed to be the appropriate subject matter of a patent; namely, processes, machines, manufactures and compositions of matter. The latter three categories define "things" while the first category defines "actions" (i.e., inventions that consist of a series of steps or acts to be performed). See 35 U.S.C. 100(b).

See MPEP 2106(IV)(A). The instant claims do not include a series of steps or acts to be performed. What the Examiner characterizes as method steps are structural limitations imposed on the claimed array. Claim 74 requires that the first nucleic acid be hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion. Thus, the limitation precludes a probe where the first nucleic acid hybridized to the second nucleic

acid forms a hybrid lacking a single-stranded portion. Similarly, claim 74 requires that the oligonucleotide be ligated to the random nucleotide sequence of the second nucleic acid. This limitation precludes the oligonucleotide from being ligated to the first nucleic acid. Further, this limitation results in a single-stranded region having a length of between about 7 to about 30 nucleotides (a random terminal nucleotide sequence of between 3-10 nucleotides in length ligated to an oligonucleotide of about 4-20 nucleotides in length). Thus, the limitations are not method steps. The limitations define certain structural attributes of the claimed array. Thus, these limitations must be accorded patentable weight and considered.

Deugau *et al.* does not disclose an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 and a longer single-stranded second nucleic acid of about 20-30 nucleotides having a random terminal nucleotide sequence of between about 3-10 nucleotides ligated to an oligonucleotide of about 4-20 nucleotides that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion.

As discussed above, Deugau *et al.* discloses that its indexing linkers are terminated by overhangs produced by cleavage with restriction endonucleases and are of a length of 3, 4, or 5 nucleotides. Deugau *et al.* does not disclose an array of probes where each probe has a double-stranded region and a single-stranded region, where the single-stranded region is greater than 5 nucleotides in length as instantly claimed (the single-stranded region includes a random terminal nucleotide sequence of between 3-10 nucleotides in length ligated to an oligonucleotide of about 4-20 nucleotides in length). Hence, Deugau *et al.* does not disclose every element of the claimed subject matter of claim 74 and its dependent claims. Thus, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 74-76, 92-94, 123, 124 and 136.

3. As directed to Claims 127-133, 135, 137 and 138

The Examiner alleges that claims 127-133, 135, 137 and 138 include "numerous method steps for making the array of probes, *e.g.* dividing the probes

and/or designing the probes and/or mental steps for defining or designing the single-stranded portions of the probe" and "that patentability of a product is based on the product, not the method of making the product" and contends that the claimed arrays are interpreted based on the resulting product. As a preliminary matter, applicant respectfully submits that none of claims 127-133, 135, 137 and 138 includes "dividing the probes" as a recitation.

The instant claims do not have method step limitations. What the Examiner characterizes as method steps are structural limitations imposed on the claimed array. For example, claim 127 requires that the probes of the array be divided into subsets, where for each subset, a selected nucleic acid base occupies a defined number of positions of the single-stranded region of the probes and all other bases except the selected base occupy the remaining positions. The limitations define certain structural attributes of the claimed array, and therefore must be accorded patentable weight and considered.

Deugau *et al.* discloses that its comprehensive panel of indexing linkers contains all possible combinations and permutations of the nucleotides A, C, G and T. Deugau *et al.* does not disclose an array of probes where within the array the probes are divided into subsets. Deugau *et al.* does not disclose a subset of probes where a selected nucleic acid base occupies a defined number of positions.

Hence, Deugau *et al.* does not disclose every element of the claimed subject matter of claim 127 and its dependent claims. Therefore, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 127-133, 135, 137 and 138.

REBUTTAL TO EXAMINER'S ARGUMENTS

"Variable" Allegedly Defined by Applicant

The Examiner alleges that the instant specification defines "variable" as varying in length, citing page 30, line 10, and thus concludes that Deugau *et al.* discloses a "variable" sequence. Applicant respectfully disagrees. The specification teaches at page 30, lines 10-14 that:

> One variable is the length of the single-stranded overhang. The shorter the overhang, the smaller the array of probes potentially useable. Overhangs of five and six have been successfully employed. The **nature of the support surface** to which the oligonucleotide is attached, the **means of its attachment**, and the **length of the oligonucleotide duplex** are **also important variables**.

Thus, the paragraph recited by the Examiner teaches that "one variable" in sequencing by hybridization is the length of the single-stranded overhang. The same paragraph teaches that other variables include the nature of the support, the means of attachment, and the length of the duplex. Further, the following paragraph teaches that "[a]nother variable is the nucleic acid capacity of the immobilized spot of probe" (see page 30, lines 18-21). Thus, the instant specification **does not** define the recitation "variable" as "varying in length" as alleged by the Examiner. Instead, the section cited by the Examiner provides a number of variables in sequencing by hybridization.

Variable Sequence of Deugau *et al.* Allegedly Not at Terminus

The Examiner alleges that

> because the single-stranded portions of Deugau *et al.* have a terminal nucleotide and the number of nucleotides between the terminal nucleotide and the double-stranded portion of the probe varies, the variable single-stranded sequence would be interpreted as being not at the terminus, but instead between the terminus and the double-stranded portion.

It appears that the Examiner is urging that the terminal nucleotide is invariable in Deugau *et al.* Applicant respectfully submits that the Examiner offers no support for this. Deugau *et al.* does not disclose that the terminal nucleotide does not vary or is in some manner held constant. Instead, Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce protruding overhangs on each end of a fragment (col. 7, lines 48-60). Further, Deugau *et al.* discloses that its comprehensive panel of indexing linkers contains all possible combinations and permutations of the nucleotides A, C, G and T. Thus, Deugau *et al.* does not disclose producing overhangs that include terminal nucleotides that do not vary or is in some manner held constant, as urged by the Examiner.

REJECTION OF CLAIMS 73, 123, 128 AND 138 UNDER 35 U.S.C. §103(a)

Claim 73, 123, 128 and 138 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deugau *et al.* in view of Brenner *et al.* (*Proc. Natl. Acad. Sci. USA*, 1989, 86:8902-8906) because Deugau *et al.* allegedly teaches every element of the claimed subject matter except the specific means by which the probes are immobilized, but Brenner *et al.* allegedly cures this defect. The Examiner alleges that Brenner *et al.* teaches that biotin/streptavidin provides a versatile means of capture immobilization.

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp*. 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

Claim 73 depends from claim 70, and claim 123 depends from claim 74. Claim 73 and claim 123 are directed to an embodiment where the probes are fixed to a solid support by conjugating to a coupling agent selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Claim 138 depends from claim 127 and is directed to an embodiment where the probes are fixed to a solid support by conjugating to a coupling agent. Claim 128 depends from claim 138 and is directed to an embodiment where the coupling agent is selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Teachings of the Cited References

Deugau *et al.*

See related section above.

Brenner *et al.*

Brenner *et al.* teaches a fluorescent DNA sequence fingerprinting procedure that couples band separation with sampled nucleotide sequencing (page 8902, right column, lines 11-14). The reference teaches cleaving DNA using endonuclease followed by electrophoresis and analysis by fluorescent emissions (paragraph bridging pages 8902-8903). Brenner *et al.* teaches that following specific cleavage using any restriction enzyme, biotin can be attached to each primary cleavage end by adding biotinylated nucleotides (page 8904, left column, second full paragraph).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Brenner *et al.* does not result in the instantly claimed arrays.

Claim 73

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of nucleic acid probes having a random sequence within the single-stranded portion that is not at the 5'-terminus or the 3'-terminus. Brenner *et al.* does not cure this defect.

Brenner *et al.* teaches a DNA fingerprinting technique that includes primary cleavage of the DNA, attaching biotin to both ends, performing a secondary cleavage, attaching the biotinylated ends to beads, labeling the ambiguous overhangs with fluorescent nucleotide-specific terminators, and eluting the labeled strands for electrophoresis (see page 8904, paragraph bridging the left and right columns and Figure 4). Brenner *et al.* does not teach or suggest a probe having a double-stranded region, a terminal single-stranded region and a random sequence within the single-stranded region that is not at the 5'-terminus or the 3'-terminus.

As shown in Figure 4, after specific cleavage, all of the resulting fragments have a single-stranded region on both ends (page 8904). Brenner *et al.* does not teach or suggest including a non-terminal random sequence within the single-stranded region. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 73.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded region and a random nucleotide sequence within the single-stranded portion that is not at the terminus. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed arrays of claim 73. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 123

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of probes where each probe has a double-stranded region and a single-stranded region, where, because a terminal nucleotide sequence of between 3-10 nucleotides is ligated to an oligonucleotide of about 4-20 nucleotides, the single-stranded region has a length of between about 7 to about 30 nucleotides.

Brenner *et al.* does not cure this defect. Brenner *et al.* teaches a DNA fingerprinting technique that includes primary cleavage of the DNA using restriction enzymes or other methods of specific cleavage, attaching biotin to both ends, performing a secondary cleavage, attaching the biotinylated ends to beads, labeling the ambiguous overhangs with fluorescent nucleotide-specific terminators, and eluting the labeled strands for electrophoresis (see page 8904, paragraph bridging the left and right columns and Figure 4). Brenner *et al.* teaches single-stranded ambiguous overhangs of 1, 2 and 4 nucleotides in length (see Fig 1., page 8903). Brenner *et al.* does not teach or suggest a probe having a double-stranded region, and a terminal single-stranded region of between about 7 to about 30 nucleotides in length. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 123.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and an oligonucleotide of about 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a

single-stranded portion; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed array of claim 123. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 128 and 138

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of probes where the probes are divided into four subsets and within each subset a selected nucleic acid base occupies a defined number of positions in the single-stranded region and bases other than the selected base occupy the remaining positions.

Brenner *et al.* does not cure this defect. Brenner *et al.* teaches using a type of restriction enzyme that leaves a 5' overhang where the sequence of the 5' overhang is not unique and can consist of several different nucleotide combinations (see page 8903, left column, last paragraph). Brenner *et al.* does not teach or suggest an array of probes that are divided into subsets. Brenner *et al.* does not teach or suggest that the single-stranded portion of each probe includes a defined number of positions occupied by a selected nucleic acid base, and all other bases except the selected base occupy the remaining positions. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 128 or 138.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the probes are divided into four subsets, where for each subset, one of the four nucleic acid bases is selected and occupies a defined number of positions in each probe and all other bases except the selected base occupy the remaining

positions. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed array of claims 128 or 138. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIMS 75 AND 132 UNDER 35 U.S.C. §103(a)

Claims 75 and 132 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deugau *et al.* in view of Ghosh *et al.* (*Nuc. Acids Research* 15: 5353-5372 (1987)) because Deugau *et al.* allegedly teaches every element of the claimed subject matter except conjugation of the probe to the support through a coupling agent, but Ghosh *et al.* allegedly cures this defect.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 75 depends from claim 74 and is directed to an embodiment where the array is fixed to a solid support selected from the group consisting of plastics, ceramics, metals, resins, gels, membranes, and chips.

Claim 132 depends from claim 127 and is directed to an embodiment where the solid support is selected from the group consisting of plastics, ceramics, metals, resins, gels, membranes, and chips.

Teachings of the Cited References

Deugau *et al.*

See related section above.

Ghosh *et al.*

Ghosh *et al.* teaches the direct covalent attachment of DNA to solid supports derivatized with alkyl-amino and alkyl-carboxylic functionalities. Ghosh *et al.* teaches covalently attaching oligonucleotides having a length of 17-29 bases to a solid support (page 5353 and page 5363) Ghosh *et al.* teaches a number of chemical methods for the attachment of DNA to solid supports through

stable covalent linkages, including carbodiimide-mediated end attachment or phosphodiester bonds (page 5354). Ghosh *et al.* teaches covalently attaching DNA oligonucleotides to solid supports by conversion to phosphoramidate derivatives that react with amino or carboxyl functionalities on the support (pages 5359-60 and 5369). Ghosh *et al.* teaches methods of preparation of phosphoramidate derivatives of the oligonucleotides (page 5358).

Ghosh *et al.* does not teach or suggest an oligonucleotide having a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. Ghosh *et al.* does not teach or suggest dividing an array of nucleic acid probes into subsets of probes where within each subset a selected nucleic acid base occupies a defined number of positions and all other bases except the selected base occupy the remaining positions in the single-stranded portion.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Ghosh *et al.* does not result in the instantly claimed arrays.

Claim 75

Claim 75 depends from claim 74 and is directed to embodiment of an array of probes each of which contains a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. As discussed above, Deugau *et al.* does not teach or suggest an array of probes each of which includes a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus.

Ghosh *et al.* does not cure this defect. Ghosh *et al.* does not teach or suggest an array of nucleic probes, nor a probe that includes a double-stranded portion, a terminal single-stranded and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. Ghosh *et al.* provides limited

information on the oligonucleotides used, teaching their length (page 5353 and page 5363) and methods of derivatizing the oligonucleotides (page 5358). Hence, even if, arguendo, Ghosh *et al.* teaches covalent coupling of oligonucleotides to a solid support, combining the teachings of Deugau *et al.* and Ghosh *et al.* does not teach or suggest every element of claim 75.

Neither Deugau *et al.* nor Ghosh *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed arrays of claim 75. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner fails to set forth a *prima facie* case of obviousness.

Claim 132

Deugau *et al.* discloses that its panel of indexing linkers contains all possible combinations and permutations of the nucleotides A, C, G and T. Deugau *et al.* does not teach or suggest an array of probes where within the array the probes are divided into four subsets. Deugau *et al.* does not teach or suggest an array of nucleic acid probes where the single-stranded portion of each probe includes a defined number of positions occupied by a base selected from the four nucleic acid bases, where the remaining positions are occupied by any of the other bases except the selected base.

Ghosh *et al.* does not cure this defect. Ghosh *et al.* does not teach or suggest an array of probes where the probes in the array are divided into four subsets. Ghosh *et al.* does not teach or suggest an array of nucleic acid probes where the probes have a single-stranded portion at one terminus and a double-stranded portion at the opposite terminus, where the single-stranded portion of each probe has a defined number of positions occupied by a selected nucleic acid base where all of the other bases except the selected base occupies the remaining positions. Hence, even if, arguendo, Ghosh *et al.* teaches covalent coupling of

oligonucleotides to a solid support, combining the teachings of Deugau *et al.* and Ghosh *et al.* does not teach or suggest every element of claim 132.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed array of claim 132. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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